

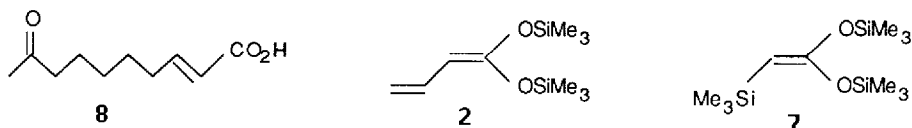
TOTAL SYNTHESIS OF QUEEN SUBSTANCE OF HONEYBEE USING AN ORGANOSILICON ROUTE[#]

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Abstract : *O-Silylated enolates are used as the key intermediates in the total synthesis of queen substance. The synthesis proceeds in 7 steps and affords the desired pheromone with very high stereoselectivity and 34% overall yield.*

The (E)-9-oxo-2-decenoic acid **8** (queen substance) has been isolated from the mandibular glands of queen honeybees¹ and synthesised². As an extension to our work concerning stereoselective aldol reactions using silylated enolates, we selected **8** as a target molecule for a total synthesis with the aim to demonstrate the utility of our organosilicon intermediates **2**^{3,4} and **7**⁵.



The central features of our strategy include :

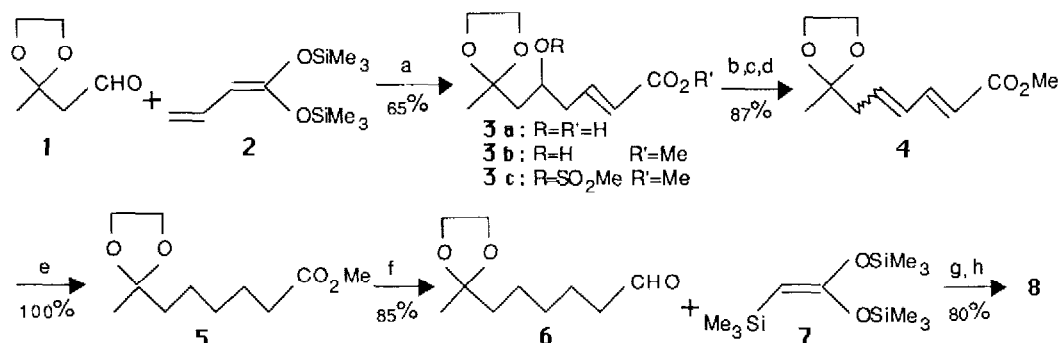
- the regio and stereocontrolled aldol reaction between aldehyde **1** and 1,1 bis(trimethylsiloxy)-1,3-butadiene **2** affording, after a series of reactions, aldehyde **6**
- a one-pot aldol reaction-Peterson olefination between the latter and C,O,O tri(trimethylsilyl) ketene acetal **7**, simultaneously setting in place the required (E)- α,β -unsaturated carboxylic acid moiety in **8**.

Aldehyde **1**⁶ is readily available from methylacetoacetate in two steps in 88% overall yield. As reported³ previously, enolisation of trimethylsilyl vinyl acetate ($\text{CH}_2=\text{CHCH}_2\text{CO}_2\text{SiMe}_3$) in THF with LDA at -78°C and quenching with ClSiMe_3 generates **2** in 90% yield. Condensation of **2** with **1** under Lewis acid conditions leads to (E)- α,β -unsaturated γ -hydroxyacid **3a** in 65% yield after purification by flash chromatography. The ^1H NMR spectrum of **3a**⁷ confirms the γ -regiospecificity and E stereoselectivity of this reaction ($J=16\text{ Hz}$).

The three step conversion of **3a** to **4** gives a mixture of E and Z isomers in 87%

[#] Warmly dedicated to Professor Marcel Gaudemar on the occasion of his 65th birthday.

overall yield. The hydrogenation of both isomers is accomplished quantitatively and subsequent reduction of **5** affords aldehyde **6** in 85% yield. **6** is treated with the silylated ketene acetal **7**⁵, easily prepared from α -trimethylsilyl trimethylsilyl acetic ester^{8,9} ($\text{Me}_3\text{SiCH}_2\text{CO}_2\text{SiMe}_3$) to give queen substance **8**¹⁰ as the single stereoisomer ($J=16$ Hz) in 80% isolated yield, after aqueous acidic hydrolysis and purification by PLC.



a) ZnBr_2 (10%), THF, RT, 24h b) CH_2N_2 , Et_2O , 0°C c) MeSO_2Cl (1eq.), NEt_3 (1.5eq.), CH_2Cl_2 , $-10^\circ\text{C} \rightarrow 0^\circ\text{C}$, 2h d) DBN (2eq.), CH_2Cl_2 , $0^\circ\text{C} \rightarrow 20^\circ\text{C}$, 2h e) H_2 , 1atms, Pd-C, AcOEt, RT, 4h f) DIBAL (1.3eq.), CH_2Cl_2 , -78°C , 1h g) CsF (2eq.), RT, 1h h) aqueous HCl 4%, acetone.

References and Notes

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- 7) Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker spectrometer (270 MHz) using TMS as an internal standard.
 ^1H NMR (CDCl_3) δ : 1.40 (3H, s), 1.85 (2H, d), 2.42 (2H, m), 4.05 (4H, s), 4.13 (1H, m), 5.93 (1H, d, $J=16$ Hz), 7.12 (1H, td, $J=16, 7$ Hz), 5.75 (2H, br, D_2O exchangeable).
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- 10) ^1H NMR (CDCl_3) δ : 1.20-1.50 (6H, m), 2.10 (3H, s), 2.20 (2H, m), 2.40 (2H, t), 5.75 (1H, d, $J=16$ Hz), 6.97 (1H, td, $J=16, 7$ Hz), 9.20 (1H, br, D_2O exchangeable).

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